



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

Date : 11/19/97
To : File
From : Mark Brunswick, Division of Monoclonal Antibodies - HFM 555
Through : Division Director, Division of Monoclonal Antibodies *K.E. Stem*
Subject : BLA 97-0260

THERAPEUTIC AGENT(S) : Rituximab (C2B8), Rituxan™
Chimeric [] antibody, [] heavy chain
constant region (Fc domain) and [] heavy and light
chain variable regions (Fab domain)
(b)(4) IgG1 κ
The target antigen is human CD-20 on human B cells

SPONSOR(S) : IDEC Pharmaceuticals
11011 Torreyana Road
San Diego
California 92121

CLINICAL INDICATION(S) : Treatment of patients with relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma (indolent lymphoma)

This review is my review of volumes 2-16 of the BLA and contains text and figures taken from the original CALA, my comments are noted as, "Reviewer note". The figures are reproduced at the end of the review as xeroxes from the BLA.

In addition, I have included information that was obtained from 2 Pre-License inspections and the following submissions:

7/1/97 Responses to 483
7/3/97 Further Responses to 483
7/8/97 Responses to Information Request Letter
8/11/97 Further Responses to Information Request Letter
8/15/97 Certificates of Analysis for 12 lots of Rituximab
8/25/97 Telcon (8/15/97) minutes
8/29/97 Micoplasma assay results and viral studies and other tests on End of Production Cells.

9/9/97 Manufacturer's commitment to answer Not Approvable Letter
10/14/97 Manufacturer's complete response to Not Approvable Letter
10/30/97 Response to Re-Inspection 483
11/5/97 Final responses to 6/97 483 observations
11/17/97 Corrections to 10/14/97 Letter
11/19/97 Methotrexate investigation

(b)(4)

PRODUCT DESCRIPTION: IDEC-C2B8 rituximab is a [] antibody that is produced in mammalian cell culture in Chinese hamster ovary (CHO) cells. The antibody binds specifically to the human CD20 antigen found on the surface of malignant and normal B cells and pre-B cells and established B-cell lines but does not react with B cell progenitors. This IgG₁ kappa antibody contains [] light and heavy chain variable regions, and human gamma 1 heavy chain (H) and kappa light chain (L) constant regions. The molecular weight of this antibody is [] Daltons, calculated from the primary sequence of the reduced, non-glycosylated form. The light chain consists of [] amino acids and the heavy chain consists of [] amino acids. Rituximab is formulated nominally at 10 mg/mL IDEC-C2B8, []

Protein Sequence of IDEC-C2B8 Light Chain:

[

18 lines

(b)(4)

]

[

4 lines

(b)(4)

]

Protein Sequence of IDEC-C2B8 Heavy Chain:

[

23 lines

(b)(4)

]

[

22 lines

(b)(4)

]

The antibody H and L chains were transfected into the Chinese hamster ovary cell line [_____]

History of the Monoclonal:

[

5 lines

]

(b)(4)

(b)(4)

diagnostic anti-CD20 antibody, [] cells secreting the anti-CD20 antibody were subsequently expanded in culture and the isotype determined to be IgG1 kappa. [] (IDEC-2B8 antibody) was selected for further study based upon the following observations:

IDEC-2B8 antibody was analyzed by immunofluorescence and found to be highly-specific for the CD20-positive cell line SB; no binding to the antigen-negative cell line HSB was detected;

IDEC-2B8 antibody effectively inhibited binding of equal concentrations of the commercially available diagnostic anti-CD20 antibodies anti-Leu 16 and B1;

IDEC-2B8 antibody recognized and bound specifically to normal human peripheral blood B lymphocytes in the same relative proportions as anti-Leu 16 and B1; and

IDEC-2B8 antibody exhibited no cross-reactivity with T lymphocyte subpopulations.

Based on these results, clone [] was chosen as the source of RNA used in isolation and construction of the murine light and heavy chain variable region genes.

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(b)(4)

THIS SECTION
WAS
DETERMINED
TO BE NOT
RELEASABLE

134 pages